

# Hexavalent Chromium: Human Data on Developmental and Reproductive Effects

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# Human Data on Developmental Effects

- Aschengrau et al. (1993): Hypothesis-generating case-control study
  - Chromium in drinking water in Boston, MA area
  - No significant association with all congenital anomalies, all stillbirths or all neonatal deaths
- Eizaguirre-Garcia *et al.* (2000): Geographical study of congenital malformations
  - Soil contamination near an old chromium-processing factory in Glasgow, Scotland
  - Significantly increased risk in those outside but not inside the center ring (radial distance from factory)
  - Assumes but doesn't show increasing exposure with distance
  - No control for maternal age or alcohol consumption



# Human Data on Female Reproductive Effects

- Shmitova (1978; 1980) [in Russian], as described by ATSDR (2000)
  - Women occupationally exposed to chromium in two facilities in Russia
  - High levels of chromium in blood and urine
  - Complications during pregnancy and childbirth at much higher rates in exposed as compared to unexposed women
  - Toxicosis; Post-natal hemorrhage
  - No conclusions can be drawn due to limited study design and reporting



# Human Data on Male Reproductive Effects

Sixteen studies of men occupationally exposed to chromium, primarily due to welding of stainless steel (SStI)

- Nine studies examining semen quality
- Seven studies examining fecundability, infertility, or male-mediated spontaneous abortion



# Exposure to Chromium During Stainless Steel Welding

- Hexavalent chromium occurs in stainless steel welding fumes
  - Varies by method and material
- To identify an effect of chromium, differences must exist in exposure levels of those being compared
  - Air or biological measurements can establish validity of comparisons
- Levels vary widely
  - Air levels: Li et al., exposed 235  $\mu\text{g}/\text{m}^3$ , unexposed 17  $\mu\text{g}/\text{m}^3$ ; Bonde studies, exposed had 2  $\mu\text{g}/\text{m}^3$



# Early Studies of Semen Quality

Study	Population	Results
Jelnes & Knudsen 1988, Denmark	77 SStl welders 68 nonwelders	No difference
Mortensen 1988, Denmark	828 men with abnormal sperm, 1689 controls	Poor sperm quality in SStl welders, OR=2.34 (0.95 – 5.73)
Tielemans et al., 1999, Netherlands	692 men with abnormal sperm, 207 controls	SStl welding not associated with increased risk



# Later Studies of Semen Quality in Denmark

Study	Population	Results
Bonde 1990a Cross-sectional in Aalborg	35 SStl welders 32 nonweld metal 22 electricians	↑ <b>Immature forms, poor motility</b> ↓ <b>Sperm count, semen volume, motile sperm</b>
Bonde 1990b Cross-sectional	18 SStl welders before & after 3 wk vacation	Improvement in sperm parameters was not significant after vacation
Hjollund et al., 1998a, Cohort	29 SStl welders 68 metal workers	No differences in semen quality or in urine levels of chromium



# More Recent Studies of Semen Quality in Asia

Study	Population	Results
Li et al., 2001 China Cross-sectional	21 electroplaters 22 unexposed	↓ <b>Sperm count, % with normal motility</b>
Danadevi et al., 2003, India Cross-sectional	57 welders 57 nonwelders	↑ <b>Abnormal morphology</b> ↓ <b>Sperm count, motility &amp; vitality</b>
Kumar et al., 2005, India Cross-sectional	61 Chromate factory workers 15 unexposed	↑ <b>Abnormal morphology</b>



# Studies of Fecundability, Infertility and Male-Mediated Spontaneous Abortion

All studies were conducted in Denmark

- Retrospective cohort – National pension records (3 studies)
- Case-control study in Aalborg
- Prospective cohort – In vitro fertilization registry
- Prospective cohort – Couples planning 1<sup>st</sup> pregnancy (2 studies)



# Retrospective Cohort – National Pension Records

Study	Population	Results
Bonde et al., 1990c	2283 ever SStI welders, compared to yrs not welding	↓ <b>Probability spouse had child when man welding</b> OR=0.91 (0.85 – 0.98)
Bonde et al., 1992b	2283 ever SStI welders, compared to yrs not welding	↑ <b>Spontaneous abortion</b> SStI welding, OR=2.0 (1.1 – 3.5)
Hjollund et al., 1995	862 pregnancies 1037 pregnancies not at risk	No increased risk of spontaneous abortion during yrs welding SStI



# Case-Control Study of Infertility & Cohort Study of In Vitro Fertilization Couples

Study	Population	Results
Bonde 1993 Case-control	52 men reporting infertility 208 men reporting no infertility	OR=2.2 (1.1 – 4.6) for any welding. Infertility reported on questionnaire
Hjollund et al., 2005 Cohort	91 SStl welders 2925 men not exposed to welding	SStl welding RR=0.59 (0.36 – 0.98) for spontaneous abortion. 85% of SStl welders welded <1 hour/day



# Prospective Cohort – Couples Planning 1<sup>st</sup> Pregnancy

Study	Population	Results
Hjollund et al., 1998b	29 SStl welders 71 nonwelders 205 nonmetal workers	<p>↓ <b>Fecundability current SStl welding:</b> OR=0.82 (0.45 – 1.50)</p> <p>↓ <b>Fecundability with ↑yrs of SStl welding:</b> 6+yr, OR=0.39 (0.18 – 0.86)</p>
Hjollund et al., 2000	29 SStl welders 71 nonwelders 205 nonmetal workers	<p>↑ <b>Spontaneous abortion</b> Current SStl welding: RR=2.6 (1.2 – 5.5).</p> <p>↑ <b>risk with yrs of SStl welding:</b> 1-5 yr, RR=1.2 (0.4 – 3.3) &gt;5 yr, RR=2.6 (1.1 – 6.1)</p>



# Summary of Human and Animal Data

## Developmental toxicity:

- *Human*: No significant effects, limited studies
- *Animal*: ↓**viability**, ↓**growth**, ↑ **anomalies**

## Female reproductive toxicity:

- *Human*: Possible effects with high exposure
- *Animal*: Effects on ovaries, estrous cycles, mating, fertility, and embryo-fetal viability

## Male reproductive toxicity:

- *Human*: Effects on sperm, ↓**fertility**, ↑**male**-mediated spontaneous abortion
- *Animal*: Effects on testes, sperm, hormones, biochemistry, and behavior

